Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Dr., rm. 1-23
Rockville, MD 20857
Docket No. 90N-0302

COMMENTS OF PUBLIC! CITIZEN LITIGATION GROUP

Public Citizen submits the following comments in response to the Food and Drug Administration's request for comments on the Interim Rule authorizing use of experimental drugs on military personnel without their informed consent, set forth at 21 C.F.R. 50.23(d). 62 Fed. Reg. 40996 (July 31, 1997). See Request for Comments, 62 Fed. Reg. 40996 (July 31, 1997). For the reasons stated in the petition submitted by Public Citizen, the National Legal Services Program, and the National Gulf War Resources Center on May 7, 1996, Public Citizen urges the FDA to repeal the Interim Rule in light of the abundant evidence that the Rule resulted in unethical and improper use of experimental drugs during the Gulf War, and because there is no evidence that the breaches of the conditions imposed on use of experimental drugs that occurred during the Gulf War would not be repeated if the Interim Rule were finalized.

Public Citizen is a non-profit public interest membership organization dedicated to the study and promotion of public health and safety and consumer welfare through lobbying, litigation, research and publications. Since its founding by Ralph Nader in 1971, Public Citizen has fought in Congress, the Food and Drug Administration, and the courts for safe, affordable and effective drugs and medical devices, for responsible controls over the delivery of health care, and for informed consent and consumer

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access to health care information. Public Citizen Health Research Group was among the parties that challenged the Interim Rule authorizing use of experimental drugs on military personnel in 1991, and Public Citizen Litigation Group represented the plaintiffs in that action. See Doe v. Sullivan, 938 F.2d 1370 (D.C. Cir. 1991).

Public Citizen requests that the comments and evidence submitted with the May 7, 1996 "Petition to Repeal Interim Rule" be incorporated and considered with the comments submitted in response to the FDA's most recent notice. Below, we specifically address the questions presented in that notice.

(1) Should the agency revoke the interim rule? If so, why?
(2) Are there circumstances under which use of the interim rule would be justified? If so, what are those circumstances?

Public Citizen believes that the interim rule should be revoked in light of the experience with the Rule during the Gulf War, and does not believe that there are any circumstances in which the waiver of informed consent permitted by the Interim Rule can be justified. The Interim Rule violates fundamental principles of medical ethics by permitting involuntary use of experimental drugs on competent, conscious military personnel. Moreover, the experience with the Interim Rule during the Gulf War shows that the conditions and requirements that the FDA used to justify the Rule -- such as requiring that troops be given some information concerning the drugs -- were not implemented and are not enforceable in practice. As a result, many military personnel were involuntarily subjected to the very risks that the requirement of informed consent is intended to protect against. In particular, we

wish to highlight three considerations that demonstrate that the Rule should be repealed.

First, the Interim Rule is inconsistent with ethical standards recognized by the FDA and enshrined in United States and international law.[1] In every other context the FDA has consistently recognized that waivers of informed consent should be limited to cases where "the investigator is not capable of obtaining consent because of inability to communicate with the patient or his representative."[2] The Interim Rule violates this ethical precept by permitting involuntary use of experimental drugs on military personnel even when it is possible to inform the personnel and obtain their consent. Moreover, this exception is not justified by the benevolent intent behind the use of the drugs or the fact that it occurs in a military context. The FDA has emphatically rejected the assertion that therapeutic use of experimental drugs does not require informed consent because of the

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[1] See, e.g., United States v. Brandt (The Medical Case) 2 Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law No. 10, pp. 181-82 (1949); Declaration of Helsinki [1975], Basic Principles, 9-11, reprinted in 21 C.F.R. 312.120 (1995); Canterbury v. Spence, 464 F.2d 772, 780 (D.C. Cir. 1972) ("'[E]very human being of adult years and sound mind has a right to determine what shall be done with his own body.'") (quoting Schloendorff v. Society of New York Hospital, 211 N.Y. 125, 105 N.E. 92, 93 (1914)).

[2] 31 Fed. Reg. 11415, 130.27(f) (1966); With the exception of the Interim Rule, the FDA also restricts waivers of informed consent to situations where the subject is "confronted by a life-threatening situation necessitating the use of" an experimental treatment and requires that there be "no equally effective approved treatment." 21 C.F.R. §§ 50.20, 50.23(a) (1997).

important rights of personal autonomy protected by this rule,[3] and these considerations apply with equal force to military personnel.

Second, when it adopted the Interim Rule the FDA maintained that waiver of informed consent was permissible because of the restrictions and safeguards imposed on use of drugs under the Rule, such as the limitation of the waiver to use on military personnel and the Commissioner's authority to require that information be given to troops on the effects of the drugs. Even if such restrictions were observed, we do not believe that they justify violating the principle of informed consent. But the Gulf War experience demonstrates that the FDA cannot count on the military to comply with such restrictions. For example, the Department of Defense concedes that it did not fulfill its commitment to provide military personnel with information on the hazards posed by the experimental drugs used during the Gulf War, information that the FDA considered essential to permit involuntary use.[4] In addition, although the waiver of informed consent was limited to use on military personnel, there have been numerous reports from civilians present in the Gulf during the War that they were given pyridostigmine bromide ("PB"), but they were not told PB was an experimental drug, nor were they informed of the potential side effects of the drug.[5]

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[3] See 44 Fed. Reg. 47718 (1979) (rejecting therapeutic use exception to informed consent); 46 Fed. Reg. 8943 (1981) (same); 60 Fed. Reg. 49087, 49088 (1995) (same).

[4] See 62 Fed. Reg. 40999-41000 (July 31, 1997).

[5] See Is Military Research Hazardous to Veterans' Health? Lessons Spanning Half a Century, S. Rep. No. 97, 103d Cong., 2d Sess. at 27 (1994) [hereinafter S. Rep. No. 97].

Third, the Gulf War experience highlights that experimental drugs pose risks that should be fully disclosed. For example, the evidence indicates that the Department of Defense failed to fully disclose the risks associated with the use of pyridostigmine bromide and that the drug may not have provided any benefit to troops, even if they had been subjected to chemical or biological weapons. In requesting that the FDA approve experimental use of PB on troops without their informed consent, DOD argued that studies with animals showed that administering PB prior to exposure to the nerve gas soman enhances the effectiveness of the two approved drugs that are administered after exposure to counteract the effects of the nerve gas, atropine and 2-PAM (pralidoxime). However, the DOD did not reveal that animal studies conducted by the military, but not yet published, showed that when nerve gases other than soman were used, pretreatment with PB actually neutralized some of the protective effects of atropine and 2-PAM.[6] Thus, if the troops been exposed to commonly-employed nerve gases sarin or VX, rather than soman, during the Gulf War, the DOD study suggests that the use of the PB actually could have caused more severe injury to the troops because the PB reduced the effectiveness of atropine and 2-PAM. Yet, neither the FDA nor the military personnel required to take the drug were informed of this risk.

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[6] Koplovitz, I., Harris, L.W., Anderson, D.R., Lennox, W.J., & Stewart, J.R. "Reduction by Pyridostigmine Pretreatment of the Efficacy of Atropine and 2-PAM Treatment of Sarin and VX Poisoning in Rodents," 18 Fundamental and Applied Toxicology, 102-06 (1992).

In short, experience shows that the Interim Rule did not work as the FDA intended and should be repealed. The Rule is inconsistent with a fundamental principle of medical ethics; the military did not comply with the safeguards the FDA offered to justify its willingness to compromise this ethical precept; and, as a result, military personnel and civilians were involuntarily and unknowingly subjected to the risks associated with these experimental drugs.

(3) The interim rule is based on the premise that informed consent is not feasible in military combat exigencies because if a soldier were permitted to say "no," this could jeopardize the individual soldier's life, endanger other personnel in his or her unit, and jeopardize the accomplishment of the combat mission. DOD has alleged that it is not an option to excuse a nonconsenting soldier from a military mission. Given the experience in the Gulf War, does this rationale still hold?

The Gulf War experience with botulinum vaccine demonstrates that this premise is false and cannot be used as a rationale for waiving the requirement of obtaining informed consent from military personnel who are conscious and able to communicate. Although the DOD represented to the FDA that it would not be feasible to obtain informed consent, once the waiver was granted, the Central Command decided that the vaccine would be given on a voluntary basis. Despite this decision, it appears that informed consent was not actually obtained from most of the 8,000 service members who received the vaccine. Nevertheless, the Central Command's decision that informed consent should be obtained demonstrates that obtaining such consent is feasible and does not jeopardize the military mission.

The Gulf War experience with PB tablets also undermines the premise of the Interim Rule. The tablets were used without

informed consent but, since these tablets were self-administered by the hundreds of thousands of troops, it was certainly feasible to inform and obtain the consent of the military personnel using the pills beforehand. Moreover, the surveys concerning the use of the PB tablets show that the requirement to take the pills was treated as voluntary within some units because a number of soldiers disregarded orders to take the tablets due to misinformation or because of the adverse side effects that they experienced.[7] Military personnel who did not take or discontinued the use of PB were not excused from their military mission.

The Gulf War experience also underscores the importance of informing subjects of the risks of experimental drugs, and giving them the opportunity to decline or discontinue using them, particularly in military combat situations. Individuals may have unique adverse reactions to experimental drugs, and studies of drugs used during the Gulf War show that a number of individuals had reactions to the drugs that affected their ability to perform in combat and, in some circumstances, led them to discontinue use of the drugs.' Military personnel facing the demands and dangers of combat certainly should be informed of the side effects that may result from the drugs that they have been given so that they can respond appropriately. Moreover, medical personnel charged with the duty of administering aid to the troops should have complete information on the effects of such drugs. Because such information

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[7] See *62* Fed. Reg. 40999.

[8] LTC Jill R. Keeler, et al., ***Pyridostigmine Used*** as ***a Nerve Agency Pretreatment*** Under ***Wartime Conditions,*** Journal of the American Medical Association, vol. 266, no. 5 (August 7, 1991).

was not provided during the Gulf War, medical personnel were not able to provide adequate treatment to military personnel suffering from adverse reactions caused by experimental drugs.

Finally, the Gulf War experience underscores that experimental drugs may have risks that are wholly unanticipated because the drugs have not been adequately tested to demonstrate their safety. For example, since the Gulf War a number of animal studies have suggested that PB used in combination with pesticides or other chemicals may create hazards that were never considered by the FDA when it approved involuntary use of this drug. This possible interaction is significant because during the Gulf War DEET and other pesticides and insect repellents were used by the same troops who were ordered to take PB. Although these studies are certainly not conclusive, they highlight that experimental drugs inherently involve unknown risks. Such risks should not be involuntarily imposed on individuals by waiving their right to informed consent.

(4) Instead of waiving the requirement for informed consent, is it feasible to obtain anticipatory consent from military personnel during peace time for the future use of investigational products during a military conflict? If it is feasible, would such consent be valid as "informed consent"? What would be the needed consent algorithm to make it valid and feasible?

(5) Instead of waiving the requirement for informed consent, is it feasible to obtain anticipatory consent from military recruits (prior to their recruitment into the military) for the future use of investigational products during a military conflict? If it is feasible, would such consent be valid? What would be the needed consent algorithm to make it valid and feasible?

Public Citizen submits that, while anticipatory consent from military personnel may be possible in theory, it is impractical in practice. To obtain effective consent, individuals would have to be fully informed of the potential risks and the context in which an investigational product may be employed, even though it may be

very difficult or impossible to anticipate and describe these conditions in advance. Moreover, the consent would need to be obtained under conditions that assured that the consent was truly voluntary, and individuals must be able to withdraw their consent if they change their minds later. Formulating, implementing and enforcing a rule that adequately addressed these issues would not be worth the effort.

Of course, it is appropriate to rely on "anticipatory consent" where an individual is unable to communicate but has previously consented to use of an experimental product. But no special military exception to the informed consent rule is necessary for these situations because they are already adequately addressed by the existing provisions of the Commission's rules.

(6) If the interim rule is needed, are there changes that should be made to it based on experiences during and following the Gulf War? If so, what are these changes and why should they be made?

(7) Can or should the interim rule be narrowed in scope? If so, how?

(8) If the rule were to be reproposed:

(a) Should there be a requirement that DOD's proposed use of the investigational product(s) be approved by an IRB that is independent of DOD? If so, why should DOD be held to a requirement not imposed on other institutions, and what should be the requirement for that independent IRB? Can this be accomplished without compromising military or national security?

(b) Should the authority to make the "feasibility determination" (i.e., whether obtaining informed consent is "not feasible") under the interim rule be vested in persons or entities other than the Commissioner of FDA?

(c) Should the rule be more specific in describing the information that must be supplied to military personnel, or should FDA have wide latitude to make such determinations on a case-by-case basis?

(d) Should additional measures be taken to insure that information required by FDA is effectively conveyed to the affected military personnel? If so, what should these measures be?

(e) Should the rule address what constitutes adequate recordkeeping and adequate long term followup of individuals who receive investigational products? If so, in what way?

(f) Should the rule contain additional procedures to enhance understanding, oversight, and accountability? If so, what are these procedures?

(g) Should the rule contain additional procedures to track noncompliance?

Public Citizen declines to address questions 6-8 because, for the reasons stated above and in the May 7, 1996 Petition, we believe that the Interim Rule is not needed and should be repealed in its entirety. Military personnel should receive the same rights of informed consent as other individuals. The Gulf War experience demonstrates that efforts to create a special military exception to the requirement of informed consent are unworkable and unwise.

Moreover, the Gulf War experience demonstrates that imposing additional procedures and restrictions is impractical because the FDA does not have the ability to monitor compliance or enforce such requirements. The waivers granted for the use of experimental drugs during the Gulf War required that specific information be distributed to military personnel, and that military investigators maintain records on the use of the investigational products. The FDA, however, does not have the ability to monitor compliance with such requirements overseas during a military conflict, and these requirements were ignored with impunity. Formalizing such requirements in the regulation is unlikely to significantly improve compliance, and certainly will not prevent military officials from disregarding such requirements if they find it to be expedient.

B. When Is It Ethical to Expose Volunteers to Toxic Chemical and Biological Agents to Test the Effectiveness of Products That May Be Used to Provide Potential Protection Against Those Agents?

The agency recognizes that reliance on nonhuman studies will almost always give greater uncertainty about effectiveness than ***would*** studies in humans. Therefore, the agency is also seeking comments on the ethical and scientific considerations of conducting human efficacy trials with these

products. For example, the agency is interested in receiving comment on whether it is ethical to conduct challenge studies in humans if, should the test product fail, there is strong reason to believe the effect of the challenge could be reversed or effectively treated. What if the effect of the challenge could not be reversed or effectively treated? What would be the needed risk/benefit assessment? Who could volunteer for such studies? Would it be ethically preferable to carry out such studies in people who could be exposed to the toxic substance? should the agency further explore these issues in a separate public forum?

The FDA should address these complex issues in a separate proceeding and a separate public forum, and should not delay a decision on repeal of the Interim Rule while it is formulating policy on these issues. The ethical issues raised by these questions are not limited to evaluation of products for use in the military context but also arise with respect to products designed to protect individuals who may be exposed to toxic substances in workplace or other situations (e.g. exposure to pesticides or industrial toxins). Consequently, these issues should be presented in a separate proceeding.

C. If Products That May Be Used to Provide Potential Protection Against Toxic Chemical and Biological Agents Cannot Be Ethically Tested in Humans, What Evidence Would Be Needed to Demonstrate Their *Safety* and Effectiveness?

(1) Should *FDA* identify the evidence needed to demonstrate safety and effectiveness for drugs that cannot ethically be tested on humans to demonstrate efficacy when such tests would involve administering a severely toxic substance to human volunteers? If "yes," what should constitute the evidence needed to demonstrate *safety and* efficacy? (The current statutory standard requires, among other things, there be "substantial evidence" that the drug is effective; "substantial evidence" means evidence "consisting of adequate and well-controlled investigations, including clinical investigations * * * on the basis of which it could fairly and responsibly be concluded by such experts that the drug" is effective.)

(2) If the agency were to identify the evidence needed to demonstrate safety and effectiveness of these products, would this preclude the need for the interim rule? What specific advantages would this offer over the interim rule?

(3) Civilian populations may require products used in the prevention or treatment of the serious or life-threatening effects

from exposure to toxic chemical or biological agents, e.g., in the event of exigencies such as the release of toxic chemical agents in the Tokyo subway system. Thus, should the agency consider identifying the evidence needed to demonstrate safety and effectiveness for these products which would apply to both civilian as well as military populations?

Public Citizen believes that the FDA should not, and cannot lawfully, establish a lower standard for evaluating the safety and effectiveness of products used on military personnel. The informed consent requirement cannot be evaded by imposing a two-tiered system in which drugs are approved for use by the military even though the evidence is insufficient to establish their safety and effectiveness under the FDA's general criteria. Both the ethical standards for informed consent and the standards for establishing safety and efficiency should apply to products used in military and civilian populations.

Respectfully submitted,

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